32 - SECTION 5 Diseases Caused by Gram-Positive Bacteria

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Gram-Positive Bacteria David Goldblatt, Katherine L. O’Brien

Pneumococcal

Infections In the late nineteenth century, pairs of micrococci were first recog nized in the blood of rabbits injected with human saliva by both Louis Pasteur, working in France, and George Sternberg, an American army physician. The important role of these micrococci in human disease was not appreciated at that time. By 1886, when the organism was designated “pneumokokkus” and Diplococcus pneumoniae, it had been isolated by many independent investigators, and its role in the etiol ogy of pneumonia was well known. In the 1930s, pneumonia was the third leading cause of death in the United States (after heart disease and cancer) and was responsible for ~7% of all deaths both in the United States and in Europe. While pneumonia was caused by a host of pathogens, lobar pneumonia—a pattern more likely to be caused by the pneumococcus—accounted for approximately one-half of all pneu monia deaths in the United States in 1929. In 1974, the organism was reclassified as Streptococcus pneumoniae. ■ ■MICROBIOLOGY Etiologic Agent Pneumococci are spherical gram-positive bacteria of the genus Streptococcus. Within this genus, cell division occurs along a single axis, and bacteria grow in chains or pairs—hence the name Streptococcus, from the Greek streptos, meaning “twisted,” and kokkos, meaning “berry.” At least 22 streptococcal species are recognized and are divided further

into groups based on their hemolytic properties. S. pneumoniae belongs to the α-hemolytic group that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin (Fig. 151-1). The bacteria are fastidious and grow best in 5% CO2 but require a source of catalase (e.g., blood) for growth on agar plates, where they develop mucoid (smooth/shiny) colonies. Pneumococci without a capsule produce colonies with a rough surface. Unlike that of other α-hemolytic streptococci, their growth is inhibited in the presence of optochin (ethylhydrocupreine hydrochloride), and they are bile soluble. In common with other gram-positive bacteria, pneumococci have a cell membrane beneath a cell wall, which in turn is covered by a polysaccharide capsule. Pneumococci are divided into serogroups or serotypes based on capsular polysaccharide structure, as distinguished with rabbit polyclonal antisera; capsules swell in the presence of spe cific antiserum (the Quellung reaction). The most recently discovered serotypes—6C, 6D, 6F, 6G, 6H, 10D, 11E, 20A, 20B, and 35D—have been identified with monoclonal antibodies and by serologic, genetic, and biochemical means. The currently recognized 100 serotypes fall

FIGURE 151-1 Pneumococci growing on blood agar, illustrating α hemolysis and optochin sensitivity (zone around optochin disk). Inset: Gram's stain, illustrating gram-positive diplococci. (Photographs courtesy of Paul Turner, University of Oxford, United Kingdom.) CHAPTER 151 into 21 serogroups, and each serogroup contains two to eight serotypes with closely related capsules. Detailed genetic analysis of the locus cod ing for the polysaccharide capsule, the cps locus, continues to reveal putative novel capsular polysaccharides, variants within existing sero groups that are designated with an "X." In the absence of type-specific antibody, the capsule protects the bacteria from phagocytosis by host cells and is arguably the most important determinant of pneumococcal virulence. Unencapsulated variants are occasionally identified in cases of invasive pneumococcal disease; however, when their genotype is assessed, they often contain capsular genes. Thus it is likely that they were encapsulated in vivo and have stopped producing capsule during the laboratory steps of pathogen isolation. Pneumococcal Infections Virulence Factors Within the cytoplasm, cell membrane, and cell wall, many molecules that may play a role in pneumococcal pathogenesis and virulence have been identified (Fig. 151-2). These proteins are often involved in direct interactions with host tissues or in concealment of the bacterial surface from host defense mechanisms. Pneumolysin (PLY) is a secreted cytotoxin thought to result in cytolysis of cells and tissues, and LytA enhances pathogenesis. A number of cell wall proteins interfere with the complement pathway, thus inhibiting complement deposition and preventing lysis and/or opsonophagocyto sis. The pneumococcal H inhibitor (Hic) impedes the formation of C3 convertase, while pneumococcal surface protein C (PspC), also known as choline-binding protein A (CbpA), binds factor H and is thought to accelerate the breakdown of C3. PspA and CbpA inhibit the deposition of or degrade C3b. To avoid clearance by the mucus, pneumococci utilize the matrix metalloprotease ZmpA, which cleaves mucosal IgA to evade complement activation, preventing agglutination and thus clearance by the mucociliary flow. The numerous pneumococcal proteins thought to be involved in adhesion include pneumococcal surface adhesin A (PsaA) and the exoglycosidases such as neuraminidase (NanA), β-galactosidase (BgaA), and β-N-Acetylglucosaminidase (StrH), which deglycosylate host glycoproteins releasing sugars as a nutrient source and expos ing hidden receptors for adhesion. Once through the epithelial bar rier, pneumococci utilize PLY and mannose receptor C type lectin 1 (MRC-1/CD206) on the surface of dendritic cells and macrophages to enter cells, where they may survive intracellularly in vacuoles thus

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